George D. Papandonatos,[1] Qing Pan,[2] Nicholas M. Pajewski,[3] Linda M. Delahanty,[4,5] Inga Peter,[6] Bahar Erar,[1] Shafqat Ahmad,[7] Maegan Harden,[8] Ling Chen,[9,10] Pierre Fontanillas,[9,10] GIANT Consortium, Lynne E. Wagenknecht,[11] Steven E. Kahn,[12] Rena R. Wing,[13] Kathleen A. Jablonski,[2] Gordon S. Huggins,[14] William C. Knowler,[15] Jose C. Florez,[4,5,9,10] Jeanne M. McCaffery,[13] and Paul W. Franks,[7,16,17] for the Diabetes Prevention Program and the Look AHEAD Research Groups*

Genetic Predisposition to Weight Loss and Regain With Lifestyle Intervention: Analyses From the Diabetes Prevention Program and the Look AHEAD Randomized Controlled Trials

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Clinically relevant weight loss is achievable through lifestyle modification, but unintentional weight regain is common. We investigated whether recently discovered genetic variants affect weight loss and/or weight regain during behavioral intervention. Participants at high-risk of type 2 diabetes (Diabetes Prevention Program [DPP]; *N* = 917/907 intervention/comparison) or with type 2 diabetes (Look AHEAD [Action for Health in Diabetes]; *N* = 2,014/1,892 intervention/comparison) were from two parallel arm (lifestyle vs. comparison) randomized controlled trials. The associations of 91 established obesity-predisposing loci with weight loss across 4 years and with weight regain across years 2–4 after a minimum of 3% weight loss were tested. Each copy of the minor G allele of *MTIF3* rs1885988 was consistently associated with greater weight loss following lifestyle intervention over 4 years across the DPP and Look AHEAD. No such effect was observed across comparison arms, leading to a nominally significant single nucleotide polymorphism×treatment interaction ($P = 4.3 \times 10^{-3}$). However, this effect was not significant at a study-wise significance level (Bonferroni threshold $P < 5.8 \times 10^{-4}$). Most obesity-predisposing gene variants were not associated with weight loss or regain within the DPP and Look AHEAD trials, directly or via interactions with lifestyle.

[1]Center for Statistical Sciences, Brown University, Providence, RI
[2]The Biostatistics Center, George Washington University, Rockville, MD
[3]Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC
[4]Diabetes Research Center (Diabetes Unit), Massachusetts General Hospital, Boston, MA
[5]Department of Medicine, Harvard Medical School, Boston, MA
[6]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY
[7]Genetic and Molecular Epidemiology Unit, Department of Clinical Sciences, Lund University, Skåne University Hospital Malmö, Malmö, Sweden
[8]Genomics Platform, Broad Institute, Cambridge, MA
[9]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA
[10]Program in Medical and Population Genetics, Broad Institute, Cambridge, MA
[11]Look AHEAD Coordinating Center, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC
[12]Division of Metabolism, Endocrinology & Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA
[13]Weight Control and Diabetes Research Center, The Miriam Hospital and The Warren Alpert Medical School of Brown University, Providence, RI
[14]Center for Translational Genomics, Molecular Cardiology Research Institute, Tufts Medical Center, Boston, MA
[15]National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ
[16]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[17]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

Corresponding authors: Paul W. Franks, paul.franks@med.lu.se and dppmail@bsc.gwu.edu, and Jeanne M. McCaffery, jeanne_mccaffery@brown.edu.

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G.D.P., J.C.F., J.M.M., and P.W.F. contributed equally to the article.

*A list of the Diabetes Prevention Program Research Group and Look AHEAD Research Group investigators is provided in the Supplementary Data online.

Adipose tissue is essential for fecundity and survival (1,2). Chronic excess adiposity (obesity) was probably uncommon throughout the majority of human evolution because foods were hunted or gathered by hand and those of very high–energy density may have been scarce. Hence, the human genome probably evolved to protect against leanness by promoting efficient energy expenditure and utilization. The heritability of BMI is ~50–90% (3), underscoring the strong, biologically encoded nature of obesity.

Recently published (4,5) large-scale meta-analyses have identified ~100 common obesogenic loci, but the clinical relevance of most of these is undetermined. Genetic data might be clinically valuable if it helped identify patients who are likely to respond well or poorly to clinical interventions, thereby facilitating targeted treatment. Testing if specific genotypes modify treatment effects in randomized controlled trials (RCTs) could help determine this.

The objective of these analyses was to test the genotype associations and treatment interactions for a comprehensive set of BMI-associated loci with intentional weight loss and weight regain in the Diabetes Prevention Program (DPP) and the Look AHEAD (Action for Health in Diabetes) studies, two RCTs of intensive lifestyle intervention conducted in multiethnic cohorts of overweight or obese adults with prediabetes or type 2 diabetes at enrollment.

RESEARCH DESIGN AND METHODS

DPP

The DPP was a 27-site multicenter parallel arm RCT that assessed the effects of metformin treatment or an intensive lifestyle intervention on type 2 diabetes incidence in persons with prediabetes at baseline. The full details of the study are published elsewhere (6,7). Briefly, a total of 3,234 overweight or obese adults with elevated fasting and postchallenge glucoses were randomized to placebo control, metformin treatment (850 mg twice daily), or intensive lifestyle intervention (primarily fat gram, calorie, and physical activity goals) aimed at ~7% weight loss. The intensive lifestyle intervention included 16 individual sessions within the first 6 months with in-person or phone follow-up at least monthly thereafter. In years 2 and beyond, group classes and campaigns were offered to reinforce lifestyle changes. In the placebo arm, standard lifestyle recommendations (annually) and inactive tablets were given. The trial's primary outcome was the development of diabetes. Numerous other phenotypes, including weight, waist circumference, and abdominal adipose tissue distribution (from CT scans), were measured at baseline and intermittently as the trial progressed; this report focuses on weight change and weight regain in the placebo control and lifestyle arms only. Analyses for a small subset of single nucleotide polymorphisms (SNPs) examined here have been published previously in the DPP (8).

DPP Participants

Prior to initiating the study protocol, each participant provided written informed consent (88% consented to genetic analyses), and each study center obtained approval from its respective institutional review board. The analytic sample for the weight-change analyses consists of 1,824 comparison and lifestyle arm participants who provided genetic consent, for whom follow-up data were available in years 1–4, and whose genotype data passed quality-control procedures. The sample used for the weight-regain analyses consisted of 834 participants who lost at least 3% of their baseline weight at 1 year and attended at least one follow-up assessment in years 2–4, consistent with prior research in the DPP (8) and Look AHEAD trials (9,10).

Look AHEAD

Look AHEAD is a 16-site multicenter parallel arm RCT designed to determine whether weight loss achieved through lifestyle change of diet and physical activity reduces cardiovascular disease morbidity and mortality among 5,145 ethnically diverse overweight or obese adults with type 2 diabetes. The full details of the study are published elsewhere (11–14). Briefly, at baseline participants were randomized to either an intensive lifestyle intervention or diabetes support and education (DSE) arm. Both the lifestyle and DSE groups were provided one session of education on diabetes and cardiovascular risk. In addition, lifestyle participants received an intensive lifestyle program (focused on achieving ~7% weight loss through calorie, fat gram, and physical activity goals) adapted from the DPP intervention. The lifestyle intervention included one individual and three group meetings per month for 6 months, followed by one individual and two group meetings per month through year 1. In years 2–4, lifestyle participants were seen individually at least monthly, contacted another time each month by telephone or e-mail, and offered a variety of group classes and campaigns, as in the DPP. The DSE group received the option of attending three sessions per year on nutrition, physical activity, and social support with no explicit weight-loss goals.

Look AHEAD Participants

Prior to initiating the study protocol, each participant provided written informed consent (84% consented to genetic analyses), and each study center obtained approval from its respective institutional review board. The analytic sample for the weight-change analyses consists of 3,906 DSE and lifestyle arm participants who provided genetic consent, for whom follow-up data were available in years 1–4, and whose genotype data passed quality-control procedures. The sample used for the weight-regain analyses consisted of 2,116 participants who lost at least 3% of their baseline weight at 1 year and attended at least one follow-up assessment in years 2–4, consistent with prior research in the DPP and Look AHEAD (8–10). Analyses for a small subset of SNPs examined here have been published previously in Look AHEAD (9,10). Both the DPP and Look AHEAD trials were conducted in accordance with the Declaration of Helsinki.

Neither the active intervention nor comparison arms of the DPP and Look AHEAD are identical. However, the active intervention in both studies represents considerably higher-intensity lifestyle interventions than were administered in the comparison arms. Therefore, for the sake of simplicity, we refer to the nonactive intervention arms of the DPP (placebo control) and Look AHEAD (DSE) as *comparison* and the active intervention arms as *lifestyle* from here on.

Genotyping

Ninety-one independent loci, characterized by 93 SNPs, identified or confirmed recently by the GIANT Consortium (5) were genotyped using the MetaboChip genotyping array (Illumina, San Diego, CA) in both studies. To ensure quality control, study participants with failed genotyping, sex inconsistency, or cryptic familial relatedness were excluded. SNPs with within-study genotyping call rates <95% or marked deviation from Hardy-Weinberg equilibrium ($P < 1.2 \times 10^{-4}$) in any ethnic group were also excluded. After quality control, the residual genotyping success rate for the 93 SNPs was >99.2% in the DPP and >99.7% in Look AHEAD (Supplementary Table 1).

Statistical Analysis

After excluding SNPs in linkage disequilibrium ($r^2 > 0.30$), EIGENSTRAT was used to compute principal components from all SNPs on the MetaboChip to control for population stratification in regression analyses. Four primary racial/ethnic groups were distinguished: non-Hispanic white, African American, Hispanic, and Asian.

Longitudinal trajectories of *1*) weight change (baseline to 1-, 2-, 3-, and 4-year postrandomization) and *2*) weight regain (year 1 to 2-, 3-, and 4-year postrandomization) among participants experiencing ≥3% weight loss from baseline to year 1 were first analyzed separately by study. Three-way interaction models of individual SNP markers (0, 1, and 2 copies of the minor allele; additive model) with study arm (lifestyle vs. comparison) and measurement time were estimated using the generalized least squares capabilities of S-Plus 8.2 (15). Three distinct types of SNP effects are presented, which can be interpreted as the effect per copy of the corresponding minor allele on *1*) time-specific weight change within lifestyle, *2*) time-specific weight change within the comparison arm, and *3*) lifestyle versus comparison arm differences in relation to time-specific weight change. Longitudinal regression models for weight-change and -regain outcomes also included adjustment for age, sex, genetic ancestry (top three principal components), clinic site, and baseline weight (for weight-loss analyses) or year 1 weight (for regain analyses). With the exception of clinic site, all the aforementioned covariates were fully interacted with time, treatment, and time by treatment, so as to allow their effects to vary across study arm and/or time point. Correlation among repeated measures on study participants and variance heteroscedasticity across time points were accommodated using an unstructured covariance matrix whose parameters were estimated via restricted maximum likelihood.

Meta-analysis

Cross-Study Differences in SNP Effects

To determine if study-specific results could be pooled, we tested for DPP versus Look AHEAD (LA) differences in SNP effects using χ^2 tests that combined information across all years of follow-up. Let $\beta_{LA} = (\beta_{LA,1}, \beta_{LA,2}, \beta_{LA,3}, \beta_{LA,4})$ and $\beta_{DPP} = (\beta_{DPP,1}, \beta_{DPP,2}, \beta_{DPP,3}, \beta_{DPP,4})$ be the study-specific parameter vectors for a particular type of SNP effect from the weight-change analysis, with elements corresponding to year-specific parameters (years 2–4 only for weight-regain analysis). We tested $H_0 : \Delta = 0$ vs. $H_1 : \Delta \neq 0$, where $\Delta = \beta_{LA} - \beta_{DPP}$. If Σ_{LA} and Σ_{DPP} represent the covariance matrices of their estimates, $\hat{\beta}_{LA}$ and $\hat{\beta}_{DPP}$, respectively, then the estimated between-study difference is $\hat{\Delta} = \hat{\beta}_{LA} - \hat{\beta}_{DPP}$ and the estimated variance of this difference is $\hat{\Sigma}_{\Delta} = \hat{\Sigma}_{LA} + \hat{\Sigma}_{DPP}$, as the estimates from the two studies are independent. Using these estimates, we used a χ^2_ν approximation of the distribution of the heterogeneity test statistic, $\hat{\Delta}'\hat{\Sigma}_{\Delta}^{-1}\hat{\Delta} \sim \chi^2_\nu$, where $\nu = 4$ for weight loss and $\nu = 3$ for weight regain.

Cross-Study Averages of SNP Effects

When no significant between-study heterogeneity was evident, pooled estimates of SNP effects across the DPP and Look AHEAD were obtained using matrix-weighted averages, which weigh study-specific estimates by their relative precision. Individual precision matrices are simply the inverses of the covariance matrices given above. On the basis of matrix-weighted averaging, the pooled estimate of each type of SNP effect was calculated as $\hat{\beta}_{pooled} = (\hat{\Sigma}_{LA}^{-1} + \hat{\Sigma}_{DPP}^{-1})^{-1}(\hat{\Sigma}_{LA}^{-1}\hat{\beta}_{LA} + \hat{\Sigma}_{DPP}^{-1}\hat{\beta}_{DPP})$. Alternatively, letting $W_{LA} = (\hat{\Sigma}_{LA}^{-1} + \hat{\Sigma}_{DPP}^{-1})^{-1}\hat{\Sigma}_{LA}^{-1}$ and $W_{DPP} = (\hat{\Sigma}_{LA}^{-1} + \hat{\Sigma}_{DPP}^{-1})^{-1}\hat{\Sigma}_{DPP}^{-1}$ be the corresponding weight matrices, we see that $\hat{\beta}_{pooled} = W_{LA}\hat{\beta}_{LA} + W_{DPP}\hat{\beta}_{DPP}$, with estimated variance $\hat{\Sigma}_{pooled} = W_{LA}\hat{\Sigma}_{LA}W'_{LA} + W_{DPP}\hat{\Sigma}_{DPP}W'_{DPP}$.

Univariate Tests of Pooled SNP Effects

To test whether the pooled estimate of a particular type of SNP effect was significantly different from zero at a specific time, $H_0 : \beta_{pooled,j} = 0$ *vs.* $H_1 : \beta_{pooled,j} \neq 0$ for $j = 1, \ldots, 4$ for weight change (or $j = 2, \ldots, 4$ for weight regain), we used a normal approximation of the distribution of the pooled test statistic, $\hat{\beta}_{pooled}/\hat{\sigma}_j \dot{\sim} N(0,1)$, where $\hat{\sigma}_j$ is the square root of the j^{th} diagonal element of $\hat{\Sigma}_{pooled}$. Identical methodology was used to test the significance of within-study effects.

Multivariate Tests of Pooled SNP Effects

To test whether the pooled estimates of a particular SNP effect were significantly different from zero across all years of follow-up, $H_0 : \beta_{pooled,j} = 0$ vs. $H_1 : \beta_{pooled,j} \neq 0$ for $j = 1, \ldots, 4$ for weight change (or $j = 2, \ldots, 4$ for weight regain), we used a χ^2 approximation of the distribution of the test statistic, $\hat{\beta}'_{pooled}\hat{\Sigma}_{pooled}^{-1}\hat{\beta}_{pooled} \dot{\sim} \chi^2_\nu$, where $\nu = 4$ for weight change and $\nu = 3$ for weight regain. Identical methodology was used to test the significance of within-study effects.

Study-wide Significance Threshold

In addition to the nominal $P < 0.05$ significance level, a multiplicity-adjusted significance threshold of $P < 5.8 \times 10^{-4}$ was derived via the Li and Ji method (16), taking into account the effective number of 88 uncorrelated markers under consideration (compared with 93 correlated ones). We note that this significance threshold corrects for the number of independent loci considered but assumes no prior probability of an effect. Hence, this may be a conservative estimate, given that these loci have known effects on BMI.

RESULTS

Participant Characteristics

Tables 1 and 2 report the demographic characteristics for both the DPP and Look AHEAD participants. Table 1 describes the sample used in the weight-change analyses (years 1–4), while Table 2 reports characteristics for the subsample used in the weight-regain analyses (years 2–4). As previously reported in the full DPP (8) and Look AHEAD (11,12,17) cohorts, both short- and long-term weight loss was greater within the lifestyle arm, as was weight regain. Supplementary Table 2 reports the associations of each SNP with baseline BMI; 17 of these SNPs were nominally associated with BMI ($P < 0.05$). Two and seven SNPs showed evidence of multiyear heterogeneity for weight loss and weight regain, respectively, across the DPP and Look AHEAD ($P < 0.05$; Supplementary Tables 3 and 4).

Weight Loss in Combined Analysis of the DPP and Look AHEAD

The intronic rs1885988 variant (at *MTIF3* and a close proxy for GIANT marker rs12016871) modified weight-loss response to lifestyle intervention (Table 3). The effect within the combined interventions reached statistical significance in year 3 ($P = 2 \times 10^{-4}$ for year 3 pooled effect within lifestyle arms), after multiple-test correction. Each copy of the minor G allele was associated with a mean −1.14 kg (95% CI −1.75, −0.53) lower weight in the lifestyle arm versus a mean 0.33 kg (−0.30, 0.95) higher weight in the comparison

Table 1—Look AHEAD and DPP (weight-loss sample) participant characteristics

	Look AHEAD			DPP		
Characteristics	Total (*N* = 3,906)	Comparison (*N* = 1,892)	Lifestyle (*N* = 2,014)	Total (*N* = 1,824)	Comparison (*N* = 907)	Lifestyle (*N* = 917)
Women (%)	2,251 (57.6)	1,081 (57.1)	1,170 (58.1)	1,241 (68.0)	623 (68.7)	618 (67.4)
Successful weight losers (%)†	2,116 (54.2)	475 (25.1)	1,641 (81.5)	834 (45.7)	201 (22.2)	633 (69.0)
Age (years)	59 (6.8)	59.1 (6.8)	58.9 (6.8)	50.7 (10.9)	50.7 (10.4)	50.7 (11.4)
Ethnicity (%)						
African American	586 (15.0)	280 (14.8)	306 (15.2)	371 (20.3)	190 (21.0)	181 (19.7)
American Indian/Alaskan Native[a]	81 (2.1)	41 (2.2)	40 (2.0)	56 (3.1)	28 (3.1)	28 (3.1)
Asian/Pacific Islander	26 (0.7)	10 (0.5)	16 (0.8)	89 (4.9)	37 (4.1)	52 (5.7)
Non-Hispanic white	2,747 (70.3)	1,350 (71.4)	1,397 (69.4)	991 (54.3)	499 (55.0)	492 (53.7)
Hispanic/Latino	392 (10.0)	173 (9.1)	219 (10.9)	317 (17.4)	153 (16.9)	164 (17.9)
Other (multiple)	74 (1.9)	38 (2.0)	36 (1.8)	—	—	—
BMI (kg/m^2)	36.1 (5.9)	36.2 (5.8)	36 (6.1)	34.1 (6.7)	34.3 (6.7)	34.0 (6.7)
Weight (kg)						
Overall Sample						
Baseline	101.8 (19.2)	102.2 (18.7)	101.4 (19.6)	94.6 (20.2)	94.8 (19.9)	94.4 (20.5)
Year 1	96.7 (19.4)	101.4 (18.9)	92.4 (18.9)	90.8 (20.5)	94.3 (20.4)	87.3 (19.9)
Year 2	97.6 (19.4)	100.9 (18.8)	94.6 (19.4)	91.6 (20.6)	94.7 (20.3)	88.5 (20.5)
Year 3	98.3 (19.5)	100.8 (19.1)	96.0 (19.6)	92.8 (21.2)	95.1 (20.4)	90.5 (21.8)
Year 4	98.4 (19.6)	100.6 (19.2)	96.3 (19.7)	94.1 (21.3)	95.6 (18.4)	92.7 (23.6)
Women						
Baseline	96.0 (17.5)	96.4 (17.4)	95.6 (17.7)	92.9 (20.4)	93.1 (20.1)	92.7 (20.7)
Year 1	91.4 (17.9)	95.6 (17.6)	87.5 (17.3)	89.2 (20.7)	92.5 (20.9)	86.0 (20.1)
Year 2	92.3 (18.0)	95.1 (17.6)	89.7 (18.0)	90.1 (20.8)	93.0 (20.6)	87.0 (20.5)
Year 3	92.8 (17.9)	94.7 (17.4)	91.1 (18.1)	91.7 (21.5)	93.4 (20.5)	90.0 (22.2)
Year 4	92.7 (17.9)	94.5 (17.7)	91.1 (18.0)	94.7 (22.5)	95.9 (18.8)	93.5 (25.5)
Men						
Baseline	109.7 (18.6)	109.8 (17.7)	109.6 (19.3)	98.3 (19.3)	98.5 (18.9)	98.1 (19.8)
Year 1	104.0 (19.0)	109.0 (17.8)	99.2 (18.9)	94.1 (19.4)	98.2 (18.7)	90.2 (19.3)
Year 2	104.9 (18.8)	108.4 (17.6)	101.4 (19.4)	94.9 (19.8)	98.4 (19.0)	91.5 (20.1)
Year 3	105.8 (19.2)	108.9 (18.2)	102.8 (19.6)	95.0 (20.6)	98.5 (19.7)	91.7 (20.9)
Year 4	106.1 (19.1)	108.8 (18.1)	103.6 (19.7)	93.0 (18.8)	94.9 (17.9)	91.2 (19.5)

All variables summarized in mean (SD) format, unless indicated otherwise. [a]The number of American Indian participants included in this study is lower than in the parent Look AHEAD trial due to lack of institutional review board approval. †This is the weight-regain analysis subsample that achieved at least 3% weight loss at year 1 (see the separate demographics table for this subsample in Table 2).

Table 2—Look AHEAD and DPP (weight-regain sample) participant characteristics

	Look AHEAD			DPP		
Characteristics	Total (*N* = 2,116)	Comparison (*N* = 475)	Lifestyle (*N* = 1,641)	Total (*N* = 834)	Comparison (*N* = 201)	Lifestyle (*N* = 633)
Women (%)	1,224 (58.0)	291 (61.3)	933 (56.9)	544 (65.2)	139 (69.2)	405 (64.0)
Age (years)	59.2 (6.8)	59.3 (6.7)	59.2 (6.9)	51.7 (11.0)	50.5 (9.6)	52.1 (11.4)
Ethnicity (%)						
African American	291 (13.8)	61 (12.8)	230 (14.0)	136 (16.3)	33 (16.4)	103 (16.3)
American Indian/Alaskan Native[a]	40 (1.9)	11 (2.3)	29 (1.8)	17 (2.0)	2 (1.0)	15 (2.4)
Asian/Pacific Islander	14 (0.7)	1 (0.2)	13 (0.8)	45 (5.4)	5 (2.5)	40 (6.3)
Non-Hispanic white	1,518 (72.0)	350 (74.0)	1,168 (71.0)	486 (58.3)	129 (64.2)	357 (56.4)
Hispanic/Latino	220 (10.4)	43 (9.1)	177 (10.8)	150 (18.0)	32 (15.9)	118 (18.6)
Other (multiple)	33 (1.6)	9 (1.9)	24 (1.5)	—	—	—
BMI (kg/m^2)	36.1 (6.1)	36.9 (6.0)	35.9 (6.1)	33.7 (6.4)	34.5 (6.7)	33.4 (6.3)
Weight (kg)						
Overall						
Baseline	102.0 (19.8)	103.8 (20.1)	101.4 (20.0)	93.7 (19.9)	95.5 (20.2)	93.1 (19.8)
Year 1	91.8 (18.5)	96.7 (18.8)	90.4 (18.2)	84.9 (18.5)	88.8 (19.4)	83.6 (18.0)
Women						
Baseline	95.9 (17.8)	97.6 (18.4)	95.3 (17.6)	91.4 (20.0)	93.2 (19.4)	90.8 (20.2)
Year 1	86.6 (16.8)	91.0 (17.2)	85.2 (16.4)	82.8 (18.6)	86.5 (19.1)	81.5 (18.3)
Men						
Baseline	110.3 (19.0)	113.4 (18.9)	109.5 (20.0)	97.9 (19.0)	100.7 (21.0)	97.2 (18.4)
Year 1	98.9 (18.4)	105.8 (17.6)	97.1 (18.2)	88.9 (17.5)	94.0 (19.4)	87.5 (16.7)
Weight regain (kg)†						
Overall						
Year 2	2.4 (5.2)	0.6 (6.4)	2.9 (4.6)	2.0 (4.2)	2.7 (4.9)	1.7 (4.0)
Year 3	3.7 (7.2)	1 (8.1)	4.5 (6.7)	3.3 (5.8)	4.2 (6.4)	3.0 (5.6)
Year 4	4.2 (8.0)	1.4 (8.5)	5.1 (7.7)	4.3 (7.7)	4.6 (9.2)	4.2 (7.2)
Women						
Year 2	2.1 (5.3)	0.2 (6.7)	2.7 (4.6)	2.1 (4.4)	2.9 (5.0)	1.8 (4.2)
Year 3	3.4 (7.1)	0.4 (8.9)	4.4 (6.1)	3.5 (6.2)	4.2 (6.9)	3.3 (6.0)
Year 4	3.8 (8.1)	0.7 (9.2)	4.8 (7.5)	4.9 (8.4)	4.4 (10.0)	5.1 (7.7)
Men						
Year 2	2.7 (5.0)	1.3 (6.0)	3.0 (4.7)	1.7 (3.8)	2.2 (4.7)	1.6 (3.6)
Year 3	4.1 (7.4)	2.0 (6.7)	4.7 (7.4)	2.8 (4.9)	4.2 (5.3)	2.4 (4.8)
Year 4	4.9 (7.8)	2.4 (7.2)	5.5 (7.8)	3.3 (6.1)	5.2 (5.9)	2.9 (6.2)

All variables summarized in mean (SD) format, unless indicated otherwise. [a]The number of American Indian participants included in this study is lower than the parent Look AHEAD trial due to lack of institutional review board approval. †Weight regain calculated as Y_j weight – Y_1 weight (kg) for j = 2, 3, 4.

arm (P = 0.30), resulting in a nominally significant interaction ($P = 9 \times 10^{-4}$ for SNP×treatment interaction at year 3). Hence, the mean differences in year-3 weight change between the lifestyle intervention and comparison arms were estimated at −1.48 kg (−2.35, −0.61) between AA homozygotes and AG heterozygotes, and −2.96 kg (−4.71, −1.22) between AA and GG homozygotes.

Longitudinal analyses (Fig. 1) showed that rs1885988 was consistently associated with weight loss within the lifestyle but not the comparison arms ($P = 2.4 \times 10^{-3}$ and P = 0.11 for multiyear tests of pooled SNP effects, respectively), leading to a consistent pattern of between-arm differences in weight change in favor of the lifestyle intervention ($P = 4.3 \times 10^{-3}$ for multiyear test of pooled SNP×treatment interaction). No other SNP×lifestyle interaction effects on weight loss showed similarly consistent patterns across all 4 years of follow-up, although several were nominally significant (Supplementary Table 3).

Weight Regain in Combined Analysis of the DPP and Look AHEAD

No SNP×treatment arm interactions reached statistical significance in longitudinal analysis after correction for multiple testing. The strongest SNP×treatment interaction was for the *FUBP1-DNAJB4* rs12401738 (P = 0.014 for multiyear test of pooled SNP×treatment interaction) (Table 3). Treatment arm–specific analyses showed that the minor allele at *FUBP1-DNAJB4* rs12401738 was consistently associated with weight regain within the comparison but not the lifestyle arms (P = 0.03 and P = 0.20 for multiyear test of pooled SNP effects, respectively) (Table 3). Specifically, each copy of the minor A allele was associated with lesser weight regain mean −0.84 kg (95% CI −1.44, −0.25) in year 2 ($P = 5.3 \times 10^{-3}$), −1.15 kg (−2.00, −0.30) in year 3 ($P = 7.7 \times 10^{-3}$), and −0.96 kg (−1.98, −0.06) in year 4 (P = 0.065) among participants within the comparison arm. Many other pooled

Table 3—Highlighted loci results for *MTIF3* (rs1885988) and weight loss over 4 years in the full sample and *FUBP1* (rs12401738) and weight regain across years 2–4 among those who lost 3% or more of their baseline weight at year 1

			Individual study results				Meta-analysis			
			Look AHEAD		DPP		Differences in estimates (LA − DPP)		Matrix-weighted averages (LA + DPP)	
Variant	Effect	Year	PE (95% CI)	*P*	PE (95% CI)	*P*	PE (95% CI)	*P*	PE (95% CI)	*P*
MTIF3 (rs1885988)	Lifestyle	1	−0.73 (−1.30, −0.15)	0.009	−0.66 (−1.45, 0.13)	0.22	−0.07 (−1.04, 0.91)	0.62	−0.70 (−1.16, −0.24)	0.002
		2	−0.95 (−1.62, −0.27)		−0.65 (−1.55, 0.25)		−0.30 (−1.42, 0.83)		−0.83 (−1.37, −0.29)	
		3	−1.18 (−1.93, −0.42)		−1.10 (−2.14, −0.06)		−0.08 (−1.36, 1.21)		−1.14 (−1.75, −0.53)	
		4	−0.54 (−1.33, 0.25)		−1.48 (−3.03, 0.08)		0.94 (−0.80, 2.68)		−0.63 (−1.30, 0.05)	
	Comparison	1	−0.36 (−0.94, 0.22)	0.09	0.68 (−0.15, 1.51)	0.34	−1.04 (−2.05, −0.03)	0.26	−0.02 (−0.50, 0.45)	0.11
		2	−0.69 (−1.36, −0.01)		0.60 (−0.34, 1.54)		−1.29 (−2.44, −0.13)		−0.25 (−0.80, 0.29)	
		3	−0.06 (−0.82, 0.70)		1.10 (−0.02, 2.21)		−1.15 (−2.50, 0.20)		0.33 (−0.30, 0.95)	
		4	−0.07 (−0.87, 0.72)		0.73 (−1.13, 2.60)		−0.81 (−2.83, 1.22)		0.24 (−0.46, 0.94)	
	Lifestyle - Comparison	1	−0.37 (−1.18, 0.44)	0.08	−1.34 (−2.48, −0.20)	0.048	0.97 (−0.43, 2.38)	0.62	−0.69 (−1.36, −0.03)	0.004
		2	−0.26 (−1.21, 0.69)		−1.25 (−2.55, 0.05)		0.99 (−0.62, 2.60)		−0.59 (−1.36, 0.17)	
		3	−1.12 (−2.19, −0.05)		−2.20 (−3.72, −0.67)		1.08 (−0.78, 2.94)		−1.48 (−2.35, −0.61)	
		4	−0.46 (−1.58, 0.66)		−2.21 (−4.63, 0.21)		1.75 (−0.92, 4.42)		−0.85 (−1.82, 0.12)	
FUBP1 (rs12401738)	Lifestyle	2	−0.12 (−0.51, 0.27)	0.24	0.51 (−0.04, 1.06)	0.27	−0.63 (−1.30, 0.05)	0.33	0.09 (−0.23, 0.41)	0.2
		3	0.06 (−0.48, 0.59)		0.70 (−0.16, 1.57)		−0.65 (−1.66, 0.37)		0.26 (−0.19, 0.72)	
		4	−0.36 (−0.96, 0.25)		0.41 (−1.04, 1.86)		−0.76 (−2.33, 0.80)		−0.16 (−0.70, 0.38)	
	Comparison	2	−0.81 (−1.55, −0.07)	0.13	−0.91 (−1.92, 0.10)	0.32	0.10 (−1.15, 1.35)	0.99	−0.84 (−1.44, −0.25)	0.03
		3	−1.12 (−2.13, −0.10)		−1.22 (−2.77, 0.32)		0.11 (−1.74, 1.96)		−1.15 (−2.00, −0.30)	
		4	−0.93 (−2.07, 0.21)		−0.98 (−3.84, 1.89)		0.05 (−3.04, 3.13)		−0.96 (−1.98, 0.06)	
	Lifestyle - Comparison	2	0.69 (−0.14, 1.52)	0.18	1.42 (0.28, 2.56)	0.08	−0.73 (−2.14, 0.69)	0.79	0.94 (0.27, 1.61)	0.01
		3	1.17 (0.02, 2.32)		1.93 (0.16, 3.69)		−0.76 (−2.87, 1.35)		1.42 (0.46, 2.38)	
		4	0.58 (−0.71, 1.86)		1.39 (−1.82, 4.6)		−0.81 (−4.27, 2.65)		0.80 (−0.35, 1.96)	

Point estimates (PE) and 95% CI represent weight change (kg) per minor allele (*MTIF3*-rs1885988 G allele; *FUBP1*-rs12401738 A allele, respectively). Longitudinal regression models adjusted for baseline weight, age, sex, ancestry (principal components 1–3), and study site. *P* values were obtained using multiyear χ^2 tests for the corresponding effect estimate. LA, Look AHEAD.

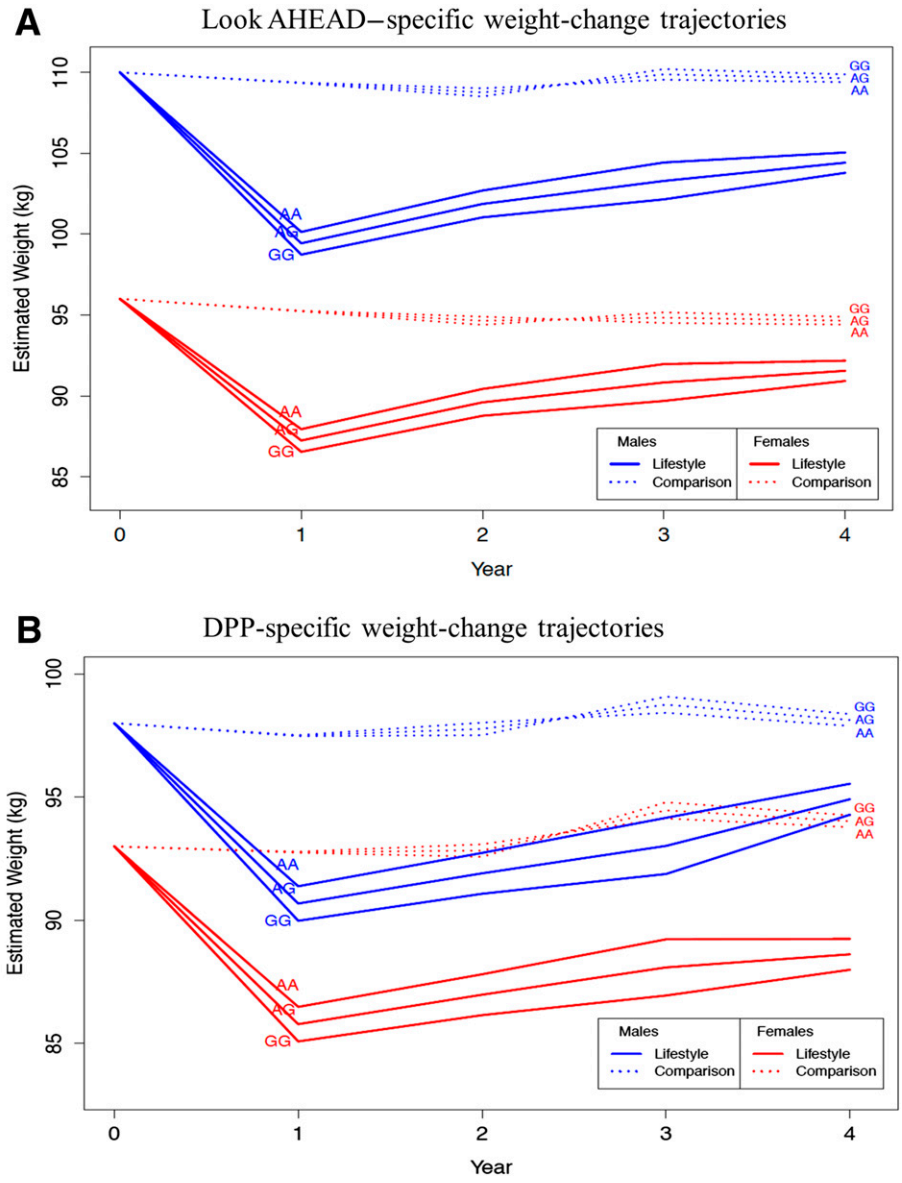

Figure 1—Model-based estimates of *MTIF3* genotype effects on weight change among 60-year-old participants following lifestyle and control intervention in the Look AHEAD (*A*) and the DPP (*B*) trials. Baseline weight chosen to be representative of males and females in each study (see Table 1). Ancestry-informative principal components set at study-specific means.

SNP×treatment interaction effects on weight regain were nominally significant within either the DPP or the Look AHEAD (Supplementary Table 4).

DISCUSSION

Many loci have been robustly associated with anthropometric indices of obesity through genome-wide association studies (GWAS) meta-analyses, revealing multiple biologic pathways (18,19). However, as these studies focused exclusively on cross-sectional epidemiological data, little is known of whether these variants influence weight change or modify the response to weight-loss interventions. Here, we sought to address these two clinically relevant questions by examining the effects of these variants on weight loss and weight regain in two large RCTs of lifestyle modification, one in people with prediabetes (DPP) and the other in patients diagnosed with type 2 diabetes prior to randomization (Look AHEAD). We found that of nearly 100 loci examined, variant rs1885988 at *MTIF3*, a close proxy for GIANT variant rs12016871, appeared to modify the effects of the lifestyle interventions on weight loss, reaching study-wide statistical significance within the lifestyle intervention arms in year 3 ($P = 2 \times 10^{-4}$) and demonstrating consistently beneficial effects across all 4 years of follow-up ($P = 2.4 \times 10^{-3}$). As no similar benefit was observed within the comparison arms, this led to a nominally significant pooled SNP×treatment interaction across all 4 years of

follow-up ($P = 4.3 \times 10^{-3}$). For weight regain, no SNPs modified treatment responses at a level reaching study-wide statistical significance. The strongest effect was observed for an SNP near *FUBP1-DNAJB4* (rs12401738), which appeared to modify the effects of the lifestyle interventions in both studies ($P_{interaction} = 0.014$) by slowing weight regain within the comparison but not the lifestyle interventions.

MTIF3 encodes a 29-kDa nuclear-encoded protein that promotes the formation of the initiation complex on the mitochondrial 55S ribosome (20,21). The mitochondrial ribosome is responsible for the synthesis of 13 of the inner mitochondrial membrane proteins and its regulation is essential for ATP synthesis, energy balance, and modulation of reactive oxygen species production in the mitochondria by the electron transport chain (21). Using the HaploReg interface (http://www.broadinstitute.org/mammals/haploreg/haploreg.php) to access the ENCODE database, we looked up the functional properties of our lead SNP (rs1885988). Although this is an intronic variant, it is 411 bp from a triallelic missense SNP with a deoxyribonuclease (DNAse) peak, with which it is in perfect linkage disequilibrium ($r^2 = 1$; $D' = 1$) in the 1000 Genomes database. Thus, the rs1885988 variant tags a chromatin site that is sensitive to transcription factor binding and hence likely regulates gene expression. We further queried the transcriptional properties of this variant in RegulomeDB (http://regulome.stanford.edu/index), which characterized the variant as a DNAse peak site in immune-regulating T cells (score 5).

A recent publication in Look AHEAD (22) examined the relationships between obesity gene variants, including *MTIF3*-rs12016871 and diet preference, but no other published studies have examined variation at this locus and lifestyle. Here, the minor G allele was associated with lifestyle-elicited weight loss in both trials and with weight regain in the DPP but not Look AHEAD. The minor G allele has previously been associated with higher BMI (18,19). Thus, carriers of the *MTIF3* obesity-inducing allele appear to benefit more from intensive lifestyle interventions than noncarriers whether they have prediabetes or overt type 2 diabetes. In a recently published, cross-sectional meta-analysis of 32 gene×dietary pattern interactions for BMI ($N > 65{,}000$) (23), the locus with the strongest signal of an interaction with a healthy diet was a close proxy of our *MTIF3* variant. The obvious differences in study design make extrapolation of those cross-sectional data to the clinical trial context difficult. However, the fact that the *MTIF3* locus was top ranked in both studies strengthens the credibility of our findings and reinforces *MTIF3* as a plausible candidate locus for gene×lifestyle interactions in obesity.

FUBP1 encodes a single-stranded DNA and RNA binding protein that regulates gene transcription, stability, and splicing (24,25), particularly for the *C-MYC* oncogene (26). Mutations at *FUPB1* are especially common in oligodendroglioma (27), a rare form of brain cancer. *DNAJB4* is preferentially expressed in heart, skeletal muscle, and pancreas and encodes a 337 amino acid heat-inducible protein (28). Expression of *DNAJB4* is associated with non–small-cell lung cancer survival (29). No publication to our knowledge has reported on the variation at *FUBP1* or *DNAJB4* and lifestyle factors in obesity or metabolic disease. In the current analyses, the minor A allele at the *FUBP1-DNAJB4* rs12401738 variant appeared to slow weight regain within the comparison arms in both trials, but not within the lifestyle arms. In the GIANT meta-analysis, the minor A allele was associated with higher BMI.

The *FTO* locus (proximal to rs9960939), which has been shown previously to interact with lifestyle factors, was not associated with weight loss directly or via treatment interactions in either the DPP (30) or Look AHEAD (10). Previously in the DPP, the *FTO* rs9939609 variant predicted a greater increase in subcutaneous adipose tissue in the placebo group compared with lifestyle intervention at year 1, but no significant genotype×treatment interaction was observed for weight loss. In Look AHEAD, several SNPs in high linkage disequilibrium showed a nominal association with weight regain at year 4 among those who had lost 3% or more of their baseline weight at year 1, but there was no effect on weight loss. The previously reported additive effect on weight change of *FTO* rs1421085 was weakened to nonsignificance in this report (from year 1–4 in the comparison arm, $P = 0.10$; treatment arm interaction, $P = 0.10$), likely due to a different subsample of Look AHEAD, including a greater representation of Native and Hispanic Americans with available MetaboChip genotyping (vs. IBC chip genotyping presented in the prior article), and to differences in analytic methods, predominantly the derivation and adjustment for new principal components from MetaboChip data to statistically adjust for ancestry. We note, however, that the effect of the lead SNP on weight regain from the prior article, *FTO* rs3751812, was maintained in this more diverse group (from year 1–4 in the comparison arm, $P = 0.02$; treatment arm interaction, $P = 0.03$). Thus, it appears that any impact of the obesity-associated region of *FTO* on weight loss following clinical intervention is weak and that larger studies designed to examine effects within racial/ethnic groups or with more detailed measurements of body composition will be needed for the effects reported here to be confirmed.

Although a handful of potential gene×treatment interaction effects are evident in these two large RCTs, one of the key findings is that the vast majority of GWAS-derived obesity-associated loci do not appear to convey clinically meaningful effects on weight loss or weight regain. This is key because many anticipate that modern population genetics research will help prevent or treat diabetes and obesity (31). Although discoveries made through GWAS meta-analyses help elucidate biological pathways, the use of individual obesity-associated SNPs derived through GWAS is unlikely to help clinicians

optimize the delivery of weight-loss interventions through targeted intervention. One possible reason that GWAS-derived loci do not serve this role well is because GWAS meta-analyses are conventionally performed without accounting for interactions with lifestyle factors and by ranking loci based solely on marginal effect *P* values, which may bias against the discovery of loci that modify the effects of lifestyle interventions (32).

The DPP and Look AHEAD are the largest existing RCTs of lifestyle intervention in people who are either at high-risk of developing or who have already developed type 2 diabetes, respectively; nevertheless, even with ~6,000 participants this analysis is likely underpowered to detect effects as small as those observed in large observational meta-analyses. However, it is unlikely these effects are clinically relevant and failing to detect them here is thus of little consequence in the context of our clinically oriented objectives. It is also important to bear in mind some key differences between the DPP and Look AHEAD trials, not least that the former focuses on people with prediabetes and the latter on people who have already developed the disease, some who are on pharmacotherapy known to influence weight. Differences in intervention protocols also exist. These factors may inhibit the detection of gene×treatment interactions. Moreover, it is likely that gene×diet interactions are nutrient specific; as such, it may be that dietary regimes that focus on different elements of the diet from the DPP and Look AHEAD interventions, such as carbohydrate or salt intake, might yield interaction effects with the variants studied here. Last, although the test of heterogeneity between the DPP and Look AHEAD suggests that there were no statistically significant differences in interaction effects between studies, it is likely that with only two studies included in this analysis the heterogeneity test was underpowered, and, as such, the absence of a significant heterogeneity test statistic should be interpreted with caution.

In conclusion, we assessed the effects on weight change of 91 established BMI-associated loci in two large RCTs of intensive lifestyle modification. The strongest association with weight loss across studies was *MTIF3*-rs1885988. Although studying BMI-associated variants derived from cross-sectional observational studies has, in this instance, provided few new insights into the genetics of behavioral weight loss and weight regain, future studies focused on genome-wide hypothesis-free discovery efforts may yield more promising results.

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Duality of Interest. L.M.D. has a financial interest in Omada Health, a company that develops online behavior-change programs, with a focus on diabetes. The interests of L.M.D. were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. P.W.F. was supported by grants from Novo Nordisk and is a member of scientific advisory boards for Eli Lilly & Co. and Sanofi Aventis. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.D.P., J.C.F., J.M.M., and P.W.F. designed the analyses and wrote the manuscript. G.D.P., Q.P., B.E., and K.A.J. undertook statistical analyses. L.M.D., L.E.W., S.E.K., R.R.W., and W.C.K. coordinated data collection. S.A., M.H., L.C., and P.F. undertook coordination tasks. All authors read and critically appraised the manuscript. G.D.P. and P.W.F. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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